CERTIFICATE OF FACSIMILE TRANSMISSION
37 C.F.R. § 1.8

I hereby certify that this correspondence is being transmitted to: Commissioner for Patents, Washington, D.C. 20231, Attn: Examiner Scott Priebe, GAU 1632, facsimile number (703) 746-3131 on the date below:

September 19, 2003
Date

Steven L. Highlander

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Dennis E. HALLAHAN *et al.*

Serial No.: 08/540,343

Filed: October 6, 1995

For: METHODS AND COMPOSITIONS FOR VIRAL ENHANCEMENT OF CELL KILLING

Group Art Unit: 1632

Examiner: S. Priebe

Atty. Dkt. No.: ARCD:194/SLH

SUPPLEMENTAL INVENTORS' DECLARATION UNDER 37 C.F.R. §1.131

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

We, the undersigned, do declare that:

1. We are citizens of the United States and named inventors on the above-captioned application.

2. A combination herpesvirus-radiation treatment of human tumor cells was performed in the United States country before June 23, 1994. Attached to this declaration is an invention disclosure prepared and signed by two of the inventors that is dated prior to June 23, 1994 (date

having been redacted). Therein, a statement is made to the effect of "HSV-1 mutants with γ34.5 deleted are inocculated into human tumors and irradiated. The combination of virus and radiation is more cytotoxic than either agent alone." Though stated in the present tense, the statement reflects experiments that had been, in fact, performed.

3. To provide additional evidence that excerpted statement from the invention disclosure describes actual experiments performed by the inventors, we also attach to this declaration notebook pages describing some of the experiments discussed in the invention disclosure. The notebook pages illustrate experiments involving infection of human tumor cells with a γ-34.5-deleted HSV-1 strain, followed by radiation treatment of these cells. Suprisingly, no cancer cell colonies were observed with the combined HSV-1/radiation treatment, which was an improvement over either treatment alone. The experiments were performed in the United States prior to June 23, 1994.

4. We hereby declare that all statements made herein of our own knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the referenced patent application or any patent issued thereon.

Date	Dr. Ralph Weichselbaum
Date	Dr. Dennis Hallahan
Date	Dr. Gregory Sibley
Date 9/6/03	Dr. Donald Kufe
Date	Dr. Bernard Roizman

4. We hereby declare that all statements made herein of our own knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the referenced patent application or any patent issued thereon.

Date	Dr. Ralph Weichselbaum
9/9/3 Date	Dennis Hallahan Dr. Dennis Hallahan
Date	Dr. Gregory Sibley
Date	Dr. Donald Kufe
Date	Dr. Bernard Roizman

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SEP.16.2003 4:57PM SIBLEY ONCOLOGY CT NO.571 P.4

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Date _____ Dr. Ralph Weichselbaum

Date _____ Dr. Dennis Hallahan

Date 9/8/03 Dr. Gregory Sibley

Date _____ Dr. Donald Kufe

Date _____ Dr. Bernard Roizman

Received 09/18/2003 13:51 in 00:42 on line [6] for SH01973 printed 09/18/2003 13:55 * Pg 2/2

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Date	Dr. Ralph Weichselbaum
Date	Dr. Dennis Hallahan
Date	Dr. Gregory Sibley
Date	Dr. Donald Kufe
Sept 18 2003 Date	Dr. Bernard Roizman

4. We hereby declare that all statements made herein of our own knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the referenced patent application or any patent issued thereon.

9/17/03
Date

Dr. Ralph Weichselbaum

Date

Dr. Dennis Hallahan

Date

Dr. Gregory Sibley

Date

Dr. Donald Kufe

Date

Dr. Bernard Roizman

DRAFT

ARCH Project Manager

University of Chicago
Confidential Invention Disclosure

UCHI # 499
Please print or type.

1. TITLE OF INVENTION/SOFTWARE

Enhancement of radiation killing with virusas

2. INVENTOR(S)/Title*	Citizenship	Dept./Campus Address	Telephone #
Dennis Hallahan, MD	US	Radiation Onc	26819
Ralph Weichselbaum, MD	US	RadiationOnc	26819
Bernard Roizman		Virology	21898

* Please attach curriculum vitae

3. DESCRIPTION OF INVENTION - Attach any additional information or background documentation.

HSV-1 mutants with γ34.5 deleted are inoculated into human tumors and irradiated. The combination of virus and radiation is more cytotoxic than either agent alone.

4. DISCLOSURE RECORD	DATE	REFERENCES & COMMENTS Use separate sheet if necessary or attach copy.
A. First oral presentation of invention at seminars, meetings, conferences, etc.	none	
B. First publication, e.g. posters, articles, abstracts, seminars	none	
C. First successful demonstration, if any (reduction to practice)		Lab notebooks
D. Other Publications to Date		
E. Anticipated Publications		

(over)

5. RESEARCH SUPPORT

A. Was the invention/discovery made in connection with any sponsored research? Yes __ No X

Sponsor | Contract/Grant # | Amount/Percent

B. If no contract or grant, was there use of University funds or facilities? Yes X No __

6. BACKGROUND RESEARCH AND PRIOR ART related to your invention: (See attached instructions)

__ No relevant prior art exists
__ See attached description
X See attached publications or references Adeno Associated Virus

7. RECORDS to substantiate your invention's history includes: (See attached instructions)

X Laboratory notes and records
__ Witnessed and Dated?
__ Financial documents
__ Dated photographs
__ Idea only
__ Rough sketches/diagrams
__ Finished, working drawings
__ Other

8. TESTING which has already been conducted includes:

__ None
X Functional testing of prototype to determine if it operates as intended
__ Market testing of invention

9. POTENTIAL LICENSEES

A. Please list any companies which you think may be interested in your invention.

Company | Address | Contact Person | Telephone #

GenVec

10. TECHNICAL/MARKETING CONTACTS (See attached instructions)

Company | Address | Contact Person | Telephone #

11. SUBMITTED BY:

Dennis Hallahan
Inventor's Signature Date

Co-Inventor's Signature Date

Co-Inventor's Signature Date

DISCLOSED TO AND UNDERSTOOD BY:

Witness' Signature Date

Witness' printed or typed name

REVIEWED BY:

Department Head Date

Printed or typed name

THE UNIVERSITY OF CHICAGO
CONFIDENTIAL INVENTION DISCLOSURE DOCUMENT

GUIDE FOR PREPARATION OF INVENTION DISCLOSURE

Completing this confidential document is the first step toward protecting and commercializing your invention. After the invention disclosure is completed, it will be recorded and filed at the Technology Center. A copy will be sent to ARCH Development Corporation (ARCH). ARCH is a non-profit affiliate of the University, and is responsible for patents, licenses and the formation of new companies at the University and Argonne National Laboratory.

The following instructions refer to the correspondingly numbered sections on the attached document.

1. Disclose only one invention. Use a separate form for each invention.

2. In naming co-inventors and co-authors, be careful to include all of those who had a creative role in the invention or software development. However, do not add names to recognize others who were not inventors or authors. Either the omission of a co-inventor/author or the inclusion of a non-inventor/author could invalidate a patent or impair a copyright.

3. Use simple language to describe your invention and define technical terms.

4. If you have published or presented this invention previously, please submit copies.

   (A) Oral presentation or publication to third parties more than one year before filing a U.S. patent application will preclude obtaining U.S. patent protection. Publication or oral presentation to third parties prior to the filing of a patent application will preclude foreign patenting.

   (B) The term "first publication" means the first time any member of the general public (without restriction of confidentiality) would have been able to legally gain access to your written or printed detailed description of the invention. (For example, the date when a journal containing your description is first mailed to the public.)

   (C) Reduction to practice occurs when an invention has been (1) embodied in some physical form which is (2) used to demonstrate its workability.

5. (A) Give the applicable contract or grant number(s) if the invention was made in connection with any sponsored research. Indicate Principal Investigators by the notation P.I.

   (B) Significant use of University-administered resources—whether funds or facilities—will normally give rise to University ownership rights in an invention. (For more details, you may request a copy of the University's Statute 20 Patents and Software policy from the Technology Center.)

6. Please provide a general description of the background research and pertinent prior work done in the field related to your invention. If possible, list five of the most relevant publications.

7. Please note all documents or forms in which your invention has been recorded or described to substantiate your invention's history, such as lab notes. Whenever possible, it is desirable to have a witness sign such documents. Actual documents may be requested if patent application is filed.

10. Please list names and telephone numbers of individuals who possess technical or marketing knowledge related to your potential application that could assist in the commercial evaluation of the invention.

11. All inventors must sign and date the disclosure form. Only persons other than co-inventors who understand the invention may serve as witnesses; departmental colleagues are excellent resources.

PLEASE SUBMIT ALL COPIES TO: The University of Chicago
Technology Center
970 E. 58th Street
Chicago, IL 60637

Questions about the invention disclosure process, contact the Technology Center, Leonora Beck 702-8606.
Questions about ARCH Development Corporation , contact Robert Nelsen, 702-0304.

2/90

HSV-1 (+) 8 37.5 + XR (3 Gy)

Variables = time (virus → XR or XR → virus) & time (XR → calcium) ie

Overnight (ON) 24h PLDR

time XR → virus -48 -24 -6 -3 -1

virus → XR +1 +3 +6 +24 +48

also time Trypsin

confluent plate = 8×10^6 cells

Plate 5×10^4, 5×10^5, 10^6 for each time

Plate 100 200 300 for PS

		5×10^4	5×10^5	10^6
ON	-48	conf	conf	conf
	-24	conf	conf	conf
	-6			
	-3	0		
	-1	0	0	0
	+1			0
	+3			
	+6	0	0	
	+24	0	0	0
	+48	0	0	0
PS:		0	0	0 !
ON	-48	conf	conf	conf
	-24 ?	conf	conf	conf
	-6	0	0	0
	-3			
	-1			0
	+1	0	0	0
	+3	0	0	
	+6	0	0	0
	+24	0	0	0

HSV on for 6h pa ?3h

PS: 5×10^4 conf — 5×10^5 conf — 10^6 10/10

-48 0 0 0

conf conf ~ NS

10^6 ~ 25 mL

HSV-1 (−) γ34.5 + XR (3 Gy)
Variables = time (virus → XR or XR → virus) & dose (XR → scheduling), no virus

Overnight (ON) 24h PLDR:

time XR → virus	−48	−24	−6	−3	−1
virus → XR	+1	+3	+6	+24	+48

same time tryp...

confluent plate = 8 x 10^6 cells

Plate 5×10^4, 5×10^5, 10^6 for each time

Plate 100 200 300 for PE

		5×10^4	5×10^5	10^6
ON	−48	conf	conf	conf
	−24	conf	conf	conf
	−6			
	−3	0		
	−1	0	0	0
	+1			0
	+3			
	+6	0	0	
	+24	0	0	0
	+48	0	0	0
	PE	0	0	0 !
0 hr	−48	conf	conf	conf
	−24 ?	conf	conf	conf
	−6	0	0	0
	−3			
	−1			0
	+1	0	0	0
	+3	0	0	0
	+6	0	0	0
	+24	0	0	0
	+48	0	0	0

HSV on for 6h on 7/31

PE: −48 5×10^4 conf → R. → 5×10^5 conf; 10^6 ~0x... ? 0

conf conf ~ 15?/10^6

conf ~200/300?

10^6 + .25 mL
5×10^4 ... mL ~ 5?/10^6
5×10^5 - 1.2 mL 0

no virus PE 100/200 · 55/100 150/300

PFU stain

75

titre		virus				
1/300	PE	(+)	37/300	44/300	410/1000	20/100
		Ø	70/300	30/100	74/200	
	3Bg	(+)	$0/10^6$	$0/10^4$	$0/10^5$	$42/10^3$
		Ø	$130/5\times10^3$	60/2000	36/1000	
1/1000	PE	(+)	40/1000	45/100		
		Ø	13/100	30/200	34/300	
	3Bg	(+)	$0/10^4$	$0/10^6$	$10/10^3$	$0/10^5$
		Ø	$300/3\times10^3$	100/2000	25/1000	

PFU/L

? Reproduces cell density dependence.
? Test dependence of ... & single dose

#	virus	dose: PE	1 Gy	3 Gy	7 Gy
40	1/200	52/100, 106/300, 108/300	10/500, 0/10^3, 0/10^4	27/10, 0/2×10^3, 0/10^4	0/10^4, 0/2×10^4, 0/10^5
"	1/2000	36/100, 94/300, 167/300	187/10^3, 0/10^4, 172/500	0/10^4, 5/200, 280/10^3	0/10^5, 40/10^4, 0/2×10^4

Decant Medium

Confluent SQ 20B
infect c̄ 40 µl (1/200)
XRay 3 Gy 6 hours after infect

Decant at 24°, 48°, feed

Primary
hardly infected > 1/200 (E1/10)

1. SQ20B
2. 18 h 1 h pulse (not free medium) → harvest after 16s ^{35}S { protein profile ③ 13 h infect
3. PE at 10^4, 10^5
4. PFU stain,
5. infect with 1 ml on shaker 1 hr

① XR → 24 + ... 13 h

→ ? could be due to ... cycling

Test other cell types: